Remarks

The Amendments

Claim 1 has been amended to specify that the claimed protease is a cysteine protease selected from the group consisting of PrtP, HagA, a HagArep peptide, a fragment or active site thereof. The amendment is made without prejudice to presenting the original claim in a continuing application. No new matter has been added by this amendment.

Claims 1, 2, and 14 have been amended to correct inadvertent errors in the claim language. The terms "protease" and "proteinase" are used in the art as interchangeable terms. Applicants have amended the claims for consistency. This amendment is not a narrowing amendment and adds no new matter.

The specification has been amended to provide explanation for arrows appearing in Figures 13 and 14. The description of Figure 13 has been amended to explain that the arrows represent occludin-stained junctions. Support for the amendment can be found in the specification at page 23, lines 15-25. The description of Figure 14 has been amended to explain that the arrows represent cadherin-stained junctions. Support for the amendment can be found in the specification at page 26, line 29 through page 27, line 7. No new matter has been added by these amendments.

Objection to the Specification

The Office has objected to the specification because the arrows in Figures 13 and 14 were not described. A description of the arrows has been added to the specification. Applicants respectfully request withdrawal of the objection.

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

Objection to Claims 5 and 16

Claims 5 and 16 have been canceled. The amendment is not a narrowing amendment made in response to a rejection. Applicants respectfully request withdrawal of the objection.

Rejection of Claims 5 and 16 Under 35 U.S.C. §112, second paragraph

Claims 5 and 16 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 5 and 16 have been canceled. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-5 and 11-16 Under 35 U.S.C. §112, first paragraph

Claims 1-5 and 11-16 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Claims 5 and 16 have been canceled. The rejection is therefore moot as applied to claims 5 and 16. Applicants respectfully traverse the rejection as it applies to claims 1-4 and 11-15.

The claims are directed to methods for the treatment or prevention of an angioproliferative condition using cysteine proteases selected from the group consisting of PrtP, HagA, a HagArep peptide, a fragment or active site thereof.

The Office Action asserts that the claims are not enabled because the specification does not provide sufficient guidance and objective evidence that the claimed methods would predictably treat or prevent an angioproliferative condition such as carcinoma. The Office Action asserts that there is no correlation between the *in vitro* and cell-based

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

assay examples of the specification and the treatment or prevention of angioproliferative conditions.

However, the use of *in vitro* tests such as inhibition of VEGF-induced proliferation of endothelial cells assays have been shown to correlate with positive clinical results with, for example, the anti-angioproliferative drug Avastin (also known as bevacizumab, anti-VEGF). *See* Presta *et al.*, J. Cancer Res. 57:4593 (1997) at page 4596, Col. 2, second full paragraph (copy attached). Avastin is an anti-angioproliferative drug that is considered to have great clinical promise. See ACS News "Drug shows promise against Avanced Colon Cancer" June, 2003 (copy attached). Therefore, inhibition of the VEGF-induced proliferation of endothelial cells assays performed with Avastin correlated with positive clinical results.

Furthermore, at the time the invention was filed, one of skill in the art at the time the invention was filed would have recognized that the inhibition of VEGF-induced proliferation of endothelial cells as a reasonably correlating example for angiogenesis. For example, Schlaeppi *et al.*, reported favorable results for anti-angiogenic compounds in VEGF-induced proliferation of endothelial cells assays. J Cancer Res Clin Oncol. 1999;125(6):336-42 (see page 340, second column, first full paragraph) (copy attached). Schlaeppi concluded that the reported anti-angiogenic compounds represented a useful agent for effective blocking of VEGF-mediated neovascularization. See Schlaeppi, page 336, abstract.

Where a particular model is recognized in the art as reasonably correlating to a specific condition, it should be accepted as correlating by the Examiner. See MPEP

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

§2164.01(c). A rigorous or an invariable exact correlation is not required. *See id.; Cross v. Iizuka*, 224 USPQ 739, 747). The art, at the time the invention was filed, recognized the VEGF-induced proliferation inhibition assay as a correlating model for anti-angiogenic compounds.

The instant invention was tested with an *in vitro* VEGF-induced proliferation inhibition assay, similar to the *in vitro* tests performed for Avastin and in Schlaeppi *et al.* *See e.g.* working Examples 1, 2, 7, and 11. Because the same *in vitro* VEGF-induced proliferation inhibition assays were performed in the instant application as were performed for Avastin and in Schlaeppi, one of skill in the art would have reasonable certainty that the claimed methods would predictably treat or prevent an angioproliferative condition, just as, e.g., Avastin does.

The Office Action further asserts that some anti-angiogenic treatments can reduce a tumor mass back to its avascular size, but they may not completely eliminate tumors. The Office Action concludes that the potential for *in vivo* micormetastasis is not eliminated. The Office Action further asserts that the latest *in vivo* testing of Endostatin has been mixed. The Office Action concludes it is therefore not predictable that a method drawn to inhibiting an angioproliferative condition would be effective in a patient suffering from cancer.

However, a reduction in tumor size or a longer survival for a cancer patient is seen as a success in the field of cancer treatment. See ACS News "Drug shows promise against advanced colon cancer" (copy attached). One of skill in the art would recognize that a "successful" anti-angiogenic treatment would not necessarily have to be a

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

complete cure for each and every patient treated. In some cases a treatment can be considered successful if it merely prolongs a patient's life for a matter months. Therefore, the fact that a complete elimination of tumors or an across-the-board cure is not expected for a certain treatment does not mean that the treatment is not useful.

The Office Action additionally asserts that reasonable guidance with respect to preventing any cancer must rely on quantitative analysis from defined populations which have been successfully pre-screened and predisposed to particular types of cancer. The Office further asserts that the essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease.

The Office appears to require detailed clinical trials on a human population in order to satisfy the enablement requirement along with an irrefutable link between antecedent drug use and subsequent knowledge of the prevention of the disease. However, such detailed and exacting data is not required for enablement. In fact, the Federal Circuit has stated that testing for full safety and effectiveness is more properly left to the FDA. *See Scott v. Finney*, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994); MPEP §2164.05.

In conclusion, the Office has cited several broad, general references stating that cancer therapy is an unpredictable art. However, Applicants have provided specific, successful working examples that use an art-recognized model for anti-angiogenesis compounds. "The evidence provided by [an] applicant need not be conclusive but merely

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

convincing to one skilled in the art." See MPEP §2164.05 (emphasis in the original). The claims are therefore enabled and Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-3, 11-14 and 16 Under 35 U.S.C. §102(b)

Claims 1-3, 11-14, and 16 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Sasisekharan *et al.* (U.S. Pat. No. 5,567,417). The rejection is moot as applied to canceled claim 16. Applicants respectfully traverse the rejection of claims 1-3 and 11-14.

Amended claims 1-3 recite methods for the treatment or prevention of an angioproliferative condition that comprises administering to a patient a pharmaceutically effective amount of a cysteine protease selected from the group consisting of PrtP, HagA, a HagArep peptide, a fragment or active site thereof. Amended claims 11-14 recite methods for selectively treating an angioproliferative condition that comprises contacting a vasculature supplying a biological structure affected by the angioproliferative condition with an angiostatically effective amount of a cysteine protease selected from the group consisting of PrtP, HagA, a HagArep peptide, a fragment or active site thereof.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990); M.P.E.P. § 2131.

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

Sasisekharan does not teach or suggest methods of use of cysteine proteases selected from the group consisting of PrtP, HagA, a HagArep peptide, a fragment or active site thereof. Sasiskharan, instead, teaches methods of use of heparinases. The substrates for heparinases are polysaccharides. See Col. 4, line 60 through Col. 5, line 15. The substrates for cysteine proteases are proteins. Therefore, heparinases and cysteine proteases are clearly two very different enzymes. Sasiskharan does not teach or suggest the use of any cysteine proteases. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-2, 5, and 11-13 Under 35 U.S.C. § 102(b)

Claims 1-2, 5, and 11-13 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Holaday *et al.* (WO 99/60984). The rejection is moot as applied to canceled claim 5. Applicants traverse the rejection as applied to claims 1-2 and 11-13.

The Office Action asserts that Holaday teaches the use of serine proteases. Serine proteases are a different class of enzymes from cysteine proteases. The active site of a serine protease includes a serine residue, a histidine residue, and an aspartate residue. During attack of the serine hydroxyl oxygen, a proton is transferred from the serine hydroxyl to the imidazole ring of the histidine, as the adjacent aspartate carboxyl is H-bonded to the histidine. The active site of a cysteine protease is a cysteine residue and a histidine residue. Cysteine proteases have a catalytic mechanism that involves a cysteine sulfhydryl group. Deprotonation of the cysteine sulfhydryl by an adjacent histidine residue is followed by nucleophilic attack of the cysteine sulfur on the peptide carbonyl carbon. Therefore, serine proteases are clearly different from cysteine protease because

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

they have different substrates. Holaday does not teach or suggest the use of any type of cysteine protease and therefore cannot anticipate the instant claims. Applicants respectfully request withdrawal of the rejection.

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

Respectfully submitted,

Date: 8/7/03 By: _____

Lisa M.W. Hillman
Reg. No. 43,673

McDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001
FACSIMILE (312) 913-0002

ACS news:

Drug Shows Promise Against Advanced Colon Cancer

Targets Tumor's Blood Supply

June 04, 2003 02:37:23 PM PST, ACS News Center

An experimental drug that targets the blood supply of tumors can help people with advanced colorectal cancer live longer, according to research presented at a recent oncology meeting. The findings give hope to scientists who have been pursuing this avenue of treatment known as antiangiogenesis therapy for years, without success.

"Our study offers important proof of the philosophy that targeting a tumor's blood supply can, in fact, inhibit the tumor's ability to proliferate," said lead investigator Herbert Hurwitz, MD, of Duke University Medical Center, in a statement.

Hurwitz and his colleagues studied more than 800 people with metastatic colorectal cancer (cancer that had spread to other parts of the body). Half the group received standard chemotherapy for their disease, while the others were treated with standard chemotherapy plus the experimental drug bevacizumab (Avastin), made by Genentech.

Patients Survived Longer

Patients receiving Avastin lived about five months longer than patients on the standard regimen alone, Hurwitz reported at the annual meeting of the American Society of Clinical Oncology in Chicago. In addition, more of the Avastin patients saw their tumors shrink, and it took longer for their tumors to resume growing.

Side effects reported in the study were not severe, the researchers said. About 11% of patients developed high blood pressure while taking Avastin, but the condition was manageable with standard medications.

The results are "extremely significant," said Durado Brooks, MD, director of prostate and colorectal cancer for the American Cancer Society. Advanced disease is very aggressive, he said, and extremely hard to treat with existing chemotherapy regimens.

"Because the outcomes are so poor with advanced disease, it's marvelous to have a new arrow in our quiver," Brooks said.

Screening Still Critical Until There's a Cure

However, he noted that Avastin is not yet available for use (a Genentech statement said it is "discussing plans" to file for FDA approval) and it isn't a cure.

"The best cure for colon cancer is not to get it," Brooks said, "so we need to be focusing on early screening to prevent it, or detect it early."

Screening can help detect colon growths called polyps before they become cancerous. With early detection, Brooks said, five-year survival of colon cancer exceeds 90%; once the disease is advanced, however, five-year survival is only about 10%. Because early colon cancer has few symptoms, only about one-third of cases are detected at this stage.

Colorectal cancer is the third most common cancer in the United States and the second leading cause of cancer deaths. The American Cancer Society estimates that more than 147,000 people will be diagnosed with it this year, and about 57,000 will die from it.

Choking the Tumor

Avastin works against colon cancer by blocking a protein called vascular endothelial growth factor (VEGF). Tumors need the protein to grow and maintain their blood vessels. When VEGF is blocked, the tumor gets less blood, so it shrinks or spreads more slowly.

Several other drugs have tried to attack cancer by choking the tumor's blood supply, but Avastin appears to be the first one that actually has succeeded, researchers said.

Scientists are hopeful that blocking VEGF can help treat other types of cancer, too. Genetech is studying Avastin for use against kidney cancer, lung cancer, and breast cancer, though initial results of a breast cancer trial were disappointing.

Results from other studies of Avastin for colorectal cancer are also expected soon.

"We want to recognize the contributions of the numerous investigators and the courage of the hundreds of patients who participated (in the clinical trials)," Genentech's chief medical officer Susan Hellmann, MD, said in a statement.